Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital

N. Fernández-Hidalgo[1,2,3], B. Almirante[1,2,3], P. Tornos[2,3,4], M. T. González-Alujas[2,3,4], A. M. Planes[3,5], M. Galiñanes[3,6] and A. Pahissa[1,2,3]

1) *Department of Infectious Diseases, Hospital Universitari Vall d'Hebron,* 2) *Department of Medicine, Universitat Autònoma de Barcelona,* 3) *Research Institute, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain,* 4) *Department of Cardiology, Hospital Universitari Vall d'Hebron,* 5) *Department of Microbiology, Hospital Universitari Vall d'Hebron and* 6) *Department of Cardiac Surgery, Hospital Universitari Vall d'Hebron*

Abstract

The aim of this study was to describe the immediate and long-term prognosis of a contemporary cohort of patients with left-sided infective endocarditis (LSIE). A prospective observational cohort study was conducted in a referral centre. Between January 2000 and December 2011, all consecutive adult patients with LSIE were followed-up until death, relapse, recurrence, need for late surgery, or last control. During the active phase of IE, 174 of 438 patients underwent surgery (40% overall; 43% native valve (NVIE), 30% prosthetic valve (PVIE)) and 125 died (29% overall; 26% NVIE, 39% PVIE). The median follow-up in survivors was 3.2 years (interquartile range (IQR) 1.0–6.0 years). Relapses occurred in seven patients (2.2%; 95% CI, 1.1–4.5) and recurrences in eight (2.6%; 95% CI, 1.3–5.0), with an incidence density of 0.0067 per patient-year (95% CI, 0.0029–0.0133) and high mortality (75% of recurrences). Only four of 130 survivors (3.1%; 95% CI, 1.2–7.6) who were treated surgically during the active phase of the disease, and 14/183 (7.7%; 95% CI, 4.6–12.4) of those not undergoing surgery needed operation during follow-up (p 0.09). In the 313 survivors, actuarial survival was 86% at 1 year (87% NVIE, 83% PVIE), 79% at 2 years (81% NVIE, 72% PVIE) and 68% at 5 years (71% NVIE, 57% PVIE). At 1 year, 115 of 397 patients (29.0%; 95% CI, 24.7–33.6) remained alive, with no surgery requirement, relapse or recurrence. LSIE is associated with considerable in-hospital and long-term mortality, especially PVIE. However, relapses, recurrences and the need for late surgery are uncommon.

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Corresponding author: N. Fernández-Hidalgo, Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain
E-mail: nufernan@gmail.com

Introduction

Infective endocarditis (IE) is a severe devastating disease, with an in-hospital mortality ranging from 17 to 30% [1–3]. Numerous contemporary studies have explored the risk factors for death in IE [1,4–6]. However, there is little information about the actual causes of in-hospital mortality in this condition [7–9] and much less effort has been dedicated to the current long-term outcome of patients surviving IE.

In 1992, our group published a 15-year cohort study describing the incidence of long-term complications of native valve IE (NVIE) in non-addicts [10], and of late prosthetic valve IE (PVIE) [11]. Since then, the epidemiology of IE has changed dramatically [12]. However, several of the related studies are not contemporary, do not differentiate between PVIE and NVIE [13,14] or between left- and right-sided IE episodes, do not distinguish between relapse and recurrence, or have several types of selection bias [13,15].

Thus, the aims of this study were to describe the causes and risk factors related to in-hospital mortality, the risk of in-hospital and 1-year mortality according to surgical indication and the long-term outcome (relapse, recurrence, need for heart surgery, and mortality) of a contemporary cohort of patients with left-sided IE.

Patients and Methods

Design, patients and settings

This prospective, observational cohort study was performed at Hospital Universitari Vall d'Hebron, a 1000-bed teaching hospital in Barcelona (Spain) with all major medical and surgical departments, and a referral centre for cardiac surgery. All consecutive adult patients (≥18 years of age) with a diagnosis of left-sided IE (LSIE) treated at our centre from January 2000 through to December 2011 were enrolled in the study. Patients were prospectively identified from the hospital Infectious Diseases, Internal Medicine, Neurology, Cardiology and Cardiac Surgery Departments, the Microbiology Department's blood culture registry, and the Echocardiography Laboratory. All interventions were performed by the same staff medical team during the entire study period, including infectious disease specialists, microbiologists, cardiologists and cardiac surgeons (endocarditis team). Every single patient was evaluated early by a cardiac surgeon in order to establish indication for surgery.

Patients who were referred for surgery from another centre at completion of antimicrobial treatment, those with non-infective endocarditis, those with pacemaker infection and no evidence of endocardial involvement and those with isolated right-sided infective endocarditis were excluded from the study. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was included in the analysis.

Definitions

Infective endocarditis was defined as definite or possible according to the modified Duke criteria [16]. Healthcare-associated IE has been defined elsewhere [4]. Late prosthetic endocarditis was defined as disease occurring more than 1 year after valve insertion. The Charlson index [17] was used at admission to stratify overall co-morbidity. The indication for surgery was established according to current and previous guidelines [18,19]. The EuroSCORE [20] was calculated for all patients with an indication for surgery. Unless otherwise specified, surgery was performed during the active phase of IE; that is, when the patient was still receiving antibiotics.

Infective endocarditis complications were defined as the development of any of the following conditions: (i) congestive heart failure (CHF; new condition or worsening of a known condition), (ii) paravalvular complication (diagnosed by echocardiography or during surgery), (iii) new conduction abnormality, (iv) stroke, (v) symptomatic systemic embolism other than stroke, and (vi) acute renal failure (ARF), established on a 25% increase in the baseline creatinine concentration.

Follow-up was defined as the period between the day after completing antimicrobial therapy to death or the last control. Relapse was established on documentation of positive blood cultures caused by the same microorganism as the initial endocarditis within the first 3 months after completing antimicrobial treatment. Recurrence was defined as new endocarditis caused by a different microorganism or infection by the same microorganism as the initial endocarditis occurring later than 3 months. Mortality was defined as death from any cause while on antimicrobial treatment (in-hospital) or during follow-up. The causes of in-hospital IE-related mortality were listed as CHF, stroke, uncontrolled infection, early postoperative death (when death occurred within 7 days after surgery), sudden death, and other causes. Non IE-related in-hospital mortality was established as death due to a cause not attributable to any IE complication in a stable IE patient with no signs of active infection (defined as negative blood cultures after starting antimicrobial treatment, and no evidence of septic metastasis or peniannular complications). Late surgery was defined as valve replacement for any reason during follow-up.

Data collection

Demographic, clinical, diagnostic, treatment and follow-up data were obtained by detailed chart abstraction with use of standardized reporting forms and were entered into a database created specifically for the purpose of this study (Microsoft Access 2000, 9.0.3821SR-I).

After completing antimicrobial therapy for IE, survivors were prospectively followed-up. Two sets of blood specimens for culture were taken 1 and 3 months later. Thereafter, patients were evaluated at regular intervals (usually every 6–12 months) at the Cardiology Outpatient Department, and at least one echocardiogram was performed within the first year. Information on later valve surgery was corroborated by means of the cardiac surgery registry. Due to the strict geographical organizational structure in our area, it is highly unlikely that patients who first attended our hospital due to an endocarditis would undergo late surgery in another centre. Late mortality data were obtained from the patients' clinical charts and were confirmed in all cases at the end of the study by consulting the regional government death registry.

Statistical analysis

Quantitative variables are reported as the median IQR and qualitative variables as the number (%). The chi-square test was used for comparing the distribution of categorical

variables and the Student *t*-test for continuous variables. For variables with a non-normal distribution, we used the Welch test. Differences were considered to be statistically significant at a p-value of <0.05. Univariate analysis was performed to assess the influence of different variables on in-hospital mortality. Variables that were determined to be clinically significant and statistically significant in the univariate analysis (p <0.1) were analysed by multivariate logistic regression analysis using a stepwise backward procedure and choosing the best model according to Mallows' Cp statistics. The goodness of fit of the final model was assessed by means of the Nagelkerke test. For the cumulative 1-year mortality, we only analysed episodes occurring before January 2011. The life-table method was used to describe long-term mortality. Differences between long-term mortality curves for NVIE and PVIE patients were analysed with the log-rank test, based on the Kaplan–Meier (product-limit) method. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL, USA).

Results

During the study period, 505 episodes of infective endocarditis in 485 patients were treated in our institution. After application of the exclusion criteria, 438 episodes of LSIE were analysed: 337 NVIE and 101 PVIE (66 late and 35 early). The general description of these cases is presented in Table 1.

In-hospital mortality and cumulative 1-year mortality

One hundred and twenty-five of 438 patients (29%) died during the active phase of infection, 86/337 (26%) with NVIE and 39/101 (39%) with PVIE. One hundred of these 125 patients (80%) died due to causes directly related to endocarditis (Table 2). Of the remaining 25 patients, 12 died due to nosocomial infection (six respiratory tract infections, two urinary tract infections, two catheter-related bacteraemia, one intra-abdominal infection and one of unknown origin), eight due to massive bleeding (four digestive, two respiratory and two other), three due to complications related to terminal cancer (one disseminated aspergillosis, one massive pulmonary thromboembolism and one respiratory insufficiency), and two cirrhotic patients due to spontaneous bacterial peritonitis.

The factors associated with in-hospital mortality in the overall series are shown in Table 3. Percentages of in-hospital and 1-year mortality according to medical or combined medical and surgical treatment for both NVIE and PVIE are summarized in Table 4.

Relapses and recurrences

After completing antimicrobial therapy, the median follow-up in survivors was 3.2 years (IQR, 1.0–6.0 years). The percentage of follow-up completeness was 97%. Nine patients were lost to follow-up after a median follow-up of 0.3 years (IQR, 0.1–5.5 years). Relapses occurred in seven patients (2.2%; 95% CI, 1.1–4.5), three in NVIE (1.2%; 95% CI, 0.4–3.5) and four in PVIE (6.5%; 95% CI, 2.5–15.4). The median time from completion of antimicrobial treatment to relapse was 25 days (IQR, 7–42 days), 12 days in NVIE (IQR, 4–16 days) and 35 days in PVIE (IQR, 26–56 days).

Recurrences were documented in eight patients (2.6%; 95% CI, 1.3–5.0), seven in NVIE (2.9%; 95% CI, 1.4–5.6) and one in PVIE (1.6%; 95% CI, 0.3–8.6). The incidence density was 0.0067 per patient-year (95% CI, 0.0029–0.0133), 0.0072 in NVIE (95% CI, 0.0029–0.0149) and 0.0046 in PVIE (95% CI, 0.0001–0.0254). Tables 5 and 6 report relapses and recurrences in detail.

Late surgery

Only four of 130 survivors (3.1%; 95% CI, 1.2–7.6) who were treated surgically during the active phase of the disease needed a second operation during follow-up, a median of 0.9 years (IQR, 0.1–1.8 years) after completing treatment: one due to relapse, one due to recurrence, and two due to progression of valve disease. None of them were re-operated on due to degeneration of a bioprosthesis previously inserted during the active phase of endocarditis. However, the percentage was 7.7% (95% CI, 4.6–12.4) (14/183) in survivors who had not undergone surgery during the first admission (p 0.087), after a median of 1.3 years (IQR, 0.1–2.9 years) following treatment. In this subgroup of patients, late surgery was performed because of recurrence in two patients and relapse in one; another patient underwent surgery after completing antimicrobial treatment because of a cerebral aneurysm. In the remaining ten patients, late surgery was performed due to progression of valve disease.

Long-term mortality

Actuarial survival for the overall series was 60% at 1 year (64% NVIE, 49% PVIE), 56% at 2 years (59% NVIE, 43% PVIE) and 48% at 5 years (52% NVIE, 34% PVIE). In the 313 patients surviving to discharge, actuarial survival was 86% at 1 year (87% NVIE, 83% PVIE), 79% at 2 years (81% NVIE, 72% PVIE) and 68% at 5 years (71% NVIE, 57% PVIE). When the mortality curves of NVIE and PVIE patients surviving the first episode were compared, clinically significant differences were found (p 0.056) (Fig. 1).

At 1 year, 115 of 397 patients (29.0%; 95% CI, 24.7–33.6) remained alive with no surgery requirement, relapse or

TABLE 1. Main epidemiological, clinical and evolutive findings of 438 episodes of left-sided infective endocarditis

Clinical characteristic	Native valve IE (*n* = 337)	Prosthetic valve IE (*n* = 101)	Overall (*n* = 438)
Age, years	65.2 (49.7–74.6)	68.7 (61.3–76.3)	66.4 (51.8–74.9)
Male sex	221 (66)	64 (63)	285 (65)
Modified Duke criteria, definite	299 (89)	87 (86)	386 (88)
Transferred from other centres	136 (40)	34 (34)	170 (39)
HAIE	94 (28)	41 (41)	135 (31)
Aortic valve affected	198 (59)	60 (59)	258 (59)
Co-morbidities			
Charlson index	1 (0–3)	2 (1–3)	2 (0–3)
Diabetes mellitus	70 (21)	29 (29)	99 (23)
Cancer	48 (14)	8 (8)	56 (13)
Immunosuppressive treatment	22 (7)	2 (2)	24 (6)
Haemodialysis	19 (6)	3 (3)	22 (5)
HIV infection	14 (4)	1 (1)	15 (3)
Intravenous drug use	11 (3)	1 (1)	12 (3)
Aetiology			
Streptococci	138 (41)	25 (25)	163 (37)
viridans-group *streptococci*	85 (25)	18 (18)	103 (24)
Streptococcus bovis	28 (8)	5 (5)	33 (8)
Other streptococci	25 (7)	2 (2)	27 (6)
Staphylococci	109 (32)	34 (34)	143 (33)
Staphylococcus aureus	85 (25)	14 (14)	99 (23)
Methicillin-resistant *S. aureus*	17/85 (20)	6/14 (43)	23/99 (23)
Coagulase-negative staphylococci	24 (7)	20 (20)	44 (10)
Enterococci	42 (13)	17 (17)	59 (14)
Gram-negative rods (GNR)	11 (3)	8 (8)	19 (4)
Non-HACEK GNR	6 (2)	4 (4)	10 (2)
HACEK group	5 (2)	4 (4)	9 (2)
Other microorganisms	20 (6)	10 (10)	30 (7)
Unknown aetiology	17 (5)	7 (7)	24 (6)
Presence of any complication	284 (84)	81 (80)	365 (83)
Congestive heart failure	166 (49)	39 (39)	205 (47)
Acute renal failure	112 (33)	40 (40)	152 (35)
Embolism other than stroke	114 (34)	19 (19)	133 (30)
Paravalvular complication	77 (23)	40 (40)	117 (27)
Stroke	69 (21)	20 (20)	89 (20)
New conduction abnormality	65 (19)	19 (19)	84 (19)
Surgery during the active phase of infection			
Indication for surgery	244 (72)	74 (73)	318 (73)
Hemodynamic	207/244 (85)	43/74 (58)	250/318 (79)
Uncontrolled infection	89/244 (37)	58/74 (78)	147/318 (46)
Embolic	120/244 (49)	27/74 (37)	147/318 (46)
Surgery performed	144 (43)	30 (30)	174 (40)
EuroSCORE when surgery performed	8 (6–11)	12.5 (11–15)	9 (9–12)
EuroSCORE when surgery indicated but not performed	10 (8–12)	13 (9–16)	11 (8–13)
Reasons for no surgery when indicated			
Good evolution without surgery	33/100 (33)	12/44 (27)	45/144 (31)
Critical status	23/100 (23)	14/44 (32)	37/144 (26)
Unaffordable surgical risk	17/100 (17)	10/44 (23)	27/144 (19)
Co-morbid basal status	18/100 (18)	5/44 (11)	23/144 (16)
Surgery scheduled after discharge	5/100 (5)	1/44 (2)	6/144 (4)
Surgeon declined to operate	2/100 (2)	2/44 (5)	4/144 (3)
Patient refused operation	2/100 (2)	–	2/144 (1)
Type of surgery			
Mechanical prosthesis	111 (77)	24 (80)	135 (78)
Bioprosthesis	30 (21)	6 (20)	36 (21)
Repair	3 (2)	–	3 (2)
Outcome			
In-hospital mortality	86 (26)	39 (39)	125 (29)
Cumulative 1-year mortality[a]	107/309 (35)	43/88 (49)	150/397 (38)
Relapse[b]	3/251 (1)	4/62 (6)	7/313 (2)
Recurrence[b]	7/251 (3)	1/62 (2)	8/313 (3)

Values are reported as *n* (%) or median (interquartile range).
IE, infective endocarditis; HAIE, healthcare-associated infective endocarditis; HIV, human immunodeficiency virus; HACEK, *Haemophilus* species, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species.
[a]Includes 397 episodes from January 2000 until December 2010.
[b]Includes 313 patients alive at the end of antimicrobial therapy.

recurrence (NVIE 85/309 (27.5%; 95% CI, 22.8–32.7), PVIE 30/88 (34.1%; 95% CI, 25.0–44.5)). At the end of follow-up, 209 patients were alive and 91 (44%) of them did not require valve surgery at any time during admission or follow-up, 64/173 (37%) with NVIE and 27/36 (75%) with PVIE.

Discussion

The overall in-hospital mortality of LSIE in this contemporary cohort was 29%, mainly due to CHF (30%) and non-IE-

TABLE 2. Causes of in-hospital mortality in 125 episodes of left-sided infective endocarditis

Cause of death	Native valve IE (*n* = 86)	Prosthetic valve IE (*n* = 39)	Overall (*n* = 125)
Congestive heart failure	26 (30)	12 (31)	38 (30)
Stroke	16 (19)	5 (13)	21 (17)
Ischaemic, *n*	8	0	8
Intracranial haemorrhage, *n*	8	5	13
Uncontrolled infection	9 (11)	8 (21)	17 (14)
Immediate post-surgical complication	8 (9)	5 (13)	13 (10)
Sudden death	5 (6)	3 (8)	8 (6)
Other IE complications	2[a] (2)	1[b] (3)	3 (2)
Death unrelated to IE	20 (23)	5 (13)	25 (20)

Values are reported as *n* (%), unless otherwise noted.
IE, infective endocarditis.
[a]Multiorgan failure due to embolic lower limb ischaemia in one, and aortic rupture 28 days after surgery in one.
[b]Multiorgan failure secondary to wound infection after lower limb amputation due to embolic ischaemia.

related causes (20%). The risk of mortality was lowest in patients who did not have an indication for surgery during the active phase of infection (13% in-hospital, 27% 1 year), and was greatest in patients in whom surgery was indicated but not performed (46% in-hospital, 58% 1 year). Relapse and recurrence were both uncommon complications in survivors (2.2% and 2.6%, respectively). For those alive at the end of antimicrobial therapy, survival was 79% and 68%, at 2 and 5 years, respectively, and the overall need for valve replacement during follow-up was 6%.

When comparing our current results with those previously reported by our group [10], we found epidemiological differences in the group of patients with NVIE. First, there was a three-fold increase in the number of NVIE cases, while during the same time period there was an ~30% increase in

TABLE 3. Univariate and multivariate analysis of in-hospital mortality in all 438 episodes of lef-sided infective endocarditis

			Univariate analysis		Multivariate analysis	
Characteristic	Alive (*n* = 313)	Dead (*n* = 125)	OR (95% CI)	p	OR (95% CI)	p
Age, years	63.9 (49.4–74.0)	70.1 (60.6–76.3)	1.03 (1.01–1.04)	0.001		
Male sex	210 (67)	75 (60)	0.7 (0.5–1.1)	0.160		
HAIE	76 (24)	59 (47)	2.8 (1.8–4.3)	<0.001	2.0 (1.1–3.6)	0.018
Prosthetic valve	62 (20)	39 (31)	1.8 (1.2–2.9)	0.011	1.9 (1.1–3.5)	0.033
Aortic valve	197 (63)	61 (49)	0.6 (0.4–0.9)	0.007		
Charlson index	1 (0–3)	2 (1–4)	1.3 (1.2–1.4)	<0.001	1.3 (1.1–1.4)	0.001
Immunosuppression	11 (4)	13 (10)	3.1 (1.4–7.3)	0.006		
Diabetes mellitus	60 (19)	39 (31)	1.9 (1.2–3.1)	0.007		
Cancer	38 (12)	18 (14)	1.2 (0.7–2.2)	0.52		
Staphylococci	77 (25)	66 (53)	3.4 (2.2–5.3)	<0.001		
Staphylococcus aureus	53 (17)	46 (37)	2.9 (1.8–4.6)	<0.001	2.0 (1.2–3.5)	0.011
MRSA	8/53 (15)	15/46 (33)	2.7 (1.0–7.2)	0.044		
Enterococci	41 (13)	18 (14)	1.1 (0.6–2.0)	0.72		
Streptococci	138 (44)	25 (20)	0.3 (0.2–0.5)	<0.001		
Any complication	241 (77)	124 (99)	37.0 (5.1–270.8)	<0.001		
ARF	79 (25)	73 (58)	4.2 (2.7–6.4)	<0.001	3.3 (1.9–5.6)	<0.001
Stroke	44 (14)	45 (36)	3.4 (2.2–5.3)	<0.001	3.8 (2.1–6.9)	<0.001
CHF	120 (38)	85 (68)	3.4 (2.1–5.6)	<0.001	3.8 (2.1–7.0)	<0.001
Surgery indicated	209 (67)	109 (87)	3.4 (1.9–6.0)	<0.001	3.2 (1.5–6.9)	0.003
Surgery not done[a]	79 (25)	65 (52)	2.4 (1.5–3.9)	<0.001		
Surgery performed	130 (42)	44 (35)	0.8 (0.5–1.2)	0.22	0.4 (0.2–0.7)	0.003

Values are reported as *n* (%) or median (interquartile range).
HAIE, healthcare-associated infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; CHF, congestive heart failure; ARF, acute renal failure.
[a]When surgery indicated.

TABLE 4. In-hospital and 1-year mortality according to medical or combined medical and surgical treatment during the active phase of infection

	In-hospital mortality			Cumulative 1-year mortality[a]		
	Overall	Native IE	Prosthetic IE	Overall	Native IE	Prosthetic IE
Surgery not indicated	16/120 (13)	15/93 (16)	1/27 (4)	29/108 (27)	27/85 (32)[b]	2/23 (9)
Surgery indicated and performed	44/174 (25)	28/144 (19)	16/30 (53)	44/155 (28)	27/129 (21)	17/26 (65)
Surgery indicated, not performed	65/144 (46)	43/100 (43)	22/44 (50)[c]	77/134 (58)	53/95 (56)	24/39 (62)[d]

Values are reported as *n*/*N* (%).
IE, infective endocarditis.
[a]Includes only 397 cases up to December 2010.
[b]Thirteen of 14 patients alive at the end of antimicrobial therapy died during the first year of follow-up due to baseline co-morbidities. The remaining patient died due to an unknown cause.
[c]Twelve of 22 patients alive at the end of antimicrobial therapy had a theoretical indication for cardiac surgery (seven isolated small (<5 mm) paravalvular abscess, three severe valve regurgitation without heart failure, and two infections caused by staphylococci), but it was not performed because of good evolution without being operated on.
[d]Eight out of 15 patients alive at 1 year had a theoretical indication for cardiac surgery (seven isolated small (<5 mm) paravalvular abscess, and one severe valve regurgitation without heart failure), but it was not performed because of good evolution without being operated on.

TABLE 5. Description of seven episodes of relapse

Age, years	Sex	Underlying condition	Aetiology	Valve affected	Surgery during active phase of IE	Days until relapse[a]	Treatment of relapse	Final status (follow-up, years)[b]
70.9	Female	Child C cirrhosis	*S. epidermidis*	Mitral prosthetic	Not performed[c]	42	Medical[d]	Alive (0.4)[e]
61.6	Male	CRF	*S. mitis*	Mitral prosthetic	Not indicated	27	Medical	Cured (0.5)
70.1	Male	CRF, stroke	*E. faecalis*	Aortic prosthetic	Not indicated	61	Medical	Cured (3.8)
88.5	Male	CRF, CPD	*E. faecalis*	Aortic prosthetic	Not performed[c]	25	Medical	Cured (1.1)
77.8	Male	Diabetes	*S. gallolyticus*	Aortic native	Not performed[f]	16	Surgical	Cured (3.3)
48.1	Male	CPD	*S. gordonii*	Mitral native	Performed[g]	4	Medical	Cured (2.2)
71.3	Female	None	c-MRSA	Mitral valve	Performed[h]	7	Surgical	Cured (0.3)

IE, infective endocarditis; CRF, chronic renal failure; CPD, chronic pulmonary disease; c-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.
[a]Days from completion of antimicrobial therapy to relapse.
[b]Years from last day of treatment to last day of follow-up.
[c]Surgery indicated but not performed because of high surgical risk.
[d]Oral suppressive antimicrobial treatment.
[e]In this case, years from start of suppressive treatment.
[f]Surgery scheduled soon after discharge.
[g]Incomplete resection of vegetations.
[h]Surgery performed 24 h after start of antimicrobial therapy.

TABLE 6. Description of eight episodes of recurrence

Age, years	Sex	Aetiology	Valve affected	Surgery during first episode	Years to recurrence[a]	Second aetiology	Valve affected second episode	Surgery during second episode	Final status (follow-up, years)[b]
66.2	Male	*S. sanguis*	Aortic native	Not performed[c]	3.7	*S. mitis*	Mitral native	Performed	Death (–)
31.0	Male	*S. mitis*	Mitral native	Not performed[d]	1.2	*Streptococcus* spp.	Mitral native	Not indicated	Death (–)
91.0	Male	*E. coli*	Mitral native	Not indicated	0.2	*Candida albicans*	Mitral native	Not performed[c]	Death (–)
72.1	Male	*S. viridans*	Mitral native	Not performed[c]	0.7	*S. epidermidis*	Mitral native	Not performed[c]	Alive (2.2)
45.1	Female	*S. mitis*	Mitral native	Not indicated	0.6	*S. mitis*	Aortic native	Not performed[e]	Death (–)
77.8	Female	*S. aureus*	Mitral native	Performed	0.3	*Candida albicans*	Mitral prosthetic	Not performed[c]	Death (–)
68.0	Male	*S. aureus*	Mitral native	Performed	0.9	*E. faecalis*	Mitral prosthetic	Performed	Alive (5.3)
77.4	Male	*S. anginosus*	Aortic native	Performed	1.7	*S. agalactiae*	Aortic prosthetic	Performed	Death (–)

[a]Years from last day of treatment of first episode to recurrence.
[b]Years from end of antimicrobial treatment for the last episode.
[c]Surgery indicated but not performed because of high surgical risk.
[d]Good evolution without surgery.
[e]End-stage multiple sclerosis.

the general population in our geographical area. Moreover, surgery and in-hospital mortality were more frequent in the contemporary group than in the early one (43% vs. 34%, p 0.087; and 26% vs. 16%, p 0.020, respectively). The median age of survivors was higher in the contemporary group (63 vs. 47 years), and there was an increase in the percentage of enterococcal (13% vs. 5%, p 0.007) and staphylococcal infections (25% vs. 8% overall, p <0.0001; 20% vs. 4% for *S. aureus*, p <0.0001), as well as higher rates of diabetes and cancer. Although relapses were similar in both groups (2.2% vs. 2.7%, p 0.378), the recurrence rate doubled in the contemporary cohort (0.0072 vs. 0.0030 episodes per person-year) and mortality was higher in recurring patients (75% vs. 20%, p 0.103). Lastly, late surgery was lower in the contemporary study than in the previous one (6% vs. 36% overall, p <0.0001), and survival was worse: 81% vs. 90% at 2 years (p 0.027) and 71% vs. 88% at 5 years (p <0.0001). Along the same lines, a recent French paper described important changes in IE epidemiology throughout the last two decades [21].

The overall in-hospital mortality in our study was high (29%), but it is the same as the value reported in another contemporary Spanish series [1]. It should be stressed that in both series the sample included all consecutive patients admitted to any hospital ward and diagnosed with infective endocarditis. In our opinion, the risk of in-hospital mortality we found was influenced by at least two factors. First, IE has undergone many epidemiological changes, as has been widely described [2,22,23], and our results corroborate this. Nowadays, about 30% of all IE episodes are associated with the healthcare system [2,4] in fragile patients, in whom the risk of death is inherently high, regardless of the type of IE, and in whom surgical decisions are particularly difficult. Second, 39% of our IE patients are transferred from community hospitals, which can negatively determine the prognosis of some patients (due to either IE-related complications or suboptimal management at origin) [24], who would benefit from specialized multidisciplinary teams [25]. In our multivariate analysis of risk factors for in-hospital mortality, the model highlighted the importance of healthcare acquisition, prosthetic valves, infection, basal co-morbid status, *S. aureus* infection, acute renal failure, stroke and congestive heart failure as risk factors for death, and the benefit of prompt surgery, in keeping with previous reports [1,2,4,26].

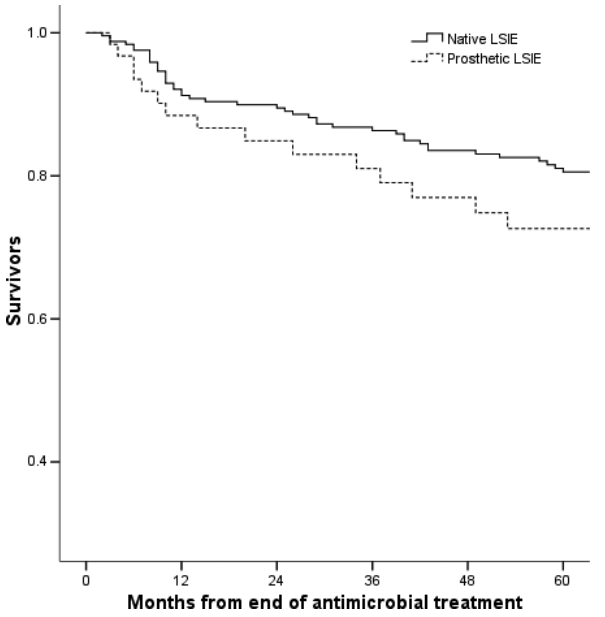

FIG. 1. Survival curve of patients alive at completion of antimicrobial therapy, according to native or prosthetic valve left-sided infective endocarditis (p 0.056). LSIE, left-sided infective endocarditis.

To the best of our knowledge, our series provides the most detailed description of in-hospital mortality in LSIE patients. Of note, 20% of patients died due to non-IE-related causes, which is consistent with a high rate of healthcare-associated infections in patients with considerable co-morbidities [9].

Although there are few randomized clinical trials regarding the influence of valve surgery on the prognosis of infective endocarditis (one of them is still recruiting patients [27] and another one is focused on young people with streptococcal IE [28]), there is growing evidence that early valve surgery is beneficial [26], especially in patients with CHF [29]. Moreover, two studies have shown that not performing surgery in patients in whom it is indicated is a risk factor for death [30,31]. In the present study, 33% of IE patients had an indication for surgery, but it was not undertaken, in most cases because of an extremely high surgical risk that contraindicated the operation. This fact perfectly explains the highest mortality in the subgroup of patients who had an indication for surgery, but in whom surgery was not performed, and the lowest in the subgroup of less severely ill patients in whom surgery was not required. However, in-hospital mortality for PVIE patients with an indication for surgery did not differ between patients undergoing surgery or not. This fact could be explained because 12 of 22 patients in this last subgroup were not surgically treated due to a good clinical evolution, thus illustrating the difficulties in establishing the criteria for surgery. On the other hand, 1-year mortality did not differ in NVIE patients not requiring surgery and those undergoing it, because of an excess of non-related IE mortality during follow-up in the former. Anyway, the analysis of the influence of surgery on mortality is always difficult, and subject to the different methodological approaches [32].

Relapses and recurrences remain as uncommon late complications of LSIE. Even though we may be faced with more difficult microorganisms and patients who cannot undergo surgery because of high surgical risk, the relapse rate has not changed in our institution, and when relapse occurs it can be successfully treated with or without surgery. Recurrences are of greater concern, because the current rate in NVIE is double that of our previous study, and recurrence is associated with high in-hospital mortality.

The need for late surgery decreased significantly from our first study [10], in which it was found that aortic valve involvement was a risk factor for requiring surgery after finalizing medical treatment. Since then, all patients with severe aortic valve regurgitation are considered for surgery during the active phase of infection regardless of whether they have CHF or not.

The incidence of late mortality was high, but as has been reported, long-term mortality does not depend on the medical or surgical treatment received during admission [15,33], but instead on baseline conditions, such as age and co-morbidities [14,34].

This study has some limitations. First, it was conducted in a referral centre, and our results may not reflect the epidemiology of community hospitals or other geographical areas. However, the single-centre design can also be considered a strength because our series was homogeneous in the treatment decisions, which were taken by a multidisciplinary team aware of the most recent developments in endocarditis and its guidelines; comparison with our earlier study illustrates the substantial epidemiological changes that have occurred in the last decades. Second, our experience is subject to referral bias due to the team's emerging profile as a centre of excellence for IE over the period of study. Third, it is possible that some cases of recurrent disease were not recorded, especially in patients who did not require cardiac surgery and were living far from the hospital. This is not the case in relapses, as blood cultures following treatment are systematically performed in our hospital. Also, there were no concerns regarding the recording of late deaths because we verified every case in the government death registry. Importantly, the percentage of cases lost to follow-up was very low in this series, an indication of the strength of the study.

In conclusion, this study, together with our previous report, shows the prognostic changes of LSIE occurring over the last 30 years. Nowadays, in-hospital and long-term

mortality rates are high, especially in PVIE, because of our patients' clinical characteristics. Even though a large number of patients could not undergo surgery, relapses were uncommon with the present approach for managing this disease, and the need for late surgery was greatly reduced. Although recurrences were infrequent, they were associated with high mortality. This fact, as well as the better prognosis of patients not needing surgery, is an indication that considerable emphasis should be placed on the prevention and prompt diagnosis of new IE episodes.

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Transparency Declaration

The authors declare no potential conflict of interests.

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